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Distal 8p Deletion (8)(p23.1): An Easily Missed Chromosomal Abnormality That May Be Associated With Congenital Heart Defect and Mental Retardation

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We describe the clinical manifestations and molecular cytogenetic analyses of three patients with a similar distal deletion of chromosome 8. Each child had mild developmental delay and subtle minor anomalies. Two had cardiac anomalies but no other major congenital anomalies were present. High resolution G and R banding showed in all three patients del(8)(p23.1), but the breakpoint in case 1 was distal to 8p23.1, in case 2 was in the middle of 8p23.1, and in case 3 proximal to 8p23.1. Fluorescence in situ hybridization (FISH) studies with a chromosome 8 paint probe confirmed that no other rearrangement had occurred. FISH with a chromosome 8-specific telomere probe indicated that two patients had terminal deletions. Chromosome analysis of the parents of case 1 and mother of case 2 were normal; the remaining parents were not available for study.

Thirteen individual patients including the three in this study, and three relatives in one family with del(8)(p23.1), have been reported in the past 5 years. Major congenital anomalies, especially congenital heart defects, are most often associated with a breakpoint proximal to 8p23.1. Three patients were found within a 3-year period in this study and five cases were found within 4 years by another group, indicating that distal 8p deletion might be a relatively common chromosomal abnormality. This small deletion is easily overlooked (i.e., cases 1 and 2 were reported as normal at amniocentesis) and can be associated with few or no major congenital anomalies. © 1996 Wiley-Liss, Inc.

KEY WORDS: chromosome 8, distal 8p deletion, del(8)(p23.1), chromosomal abnormality, congenital heart defects, mental retardation, facial anomalies, developmental delay

INTRODUCTION

The first case of an 8p deletion, del(8)(p21→pter), was described by Lubs and Lubs in 1973. Since then, more than 30 cases of various 8p deletions, either terminal or interstitial, have been reported [Taillemite et al., 1975; de la Chapelle et al., 1976; Orye and Craen et al., 1976; Beighle et al., 1977; Bresson et al., 1977; Leisti and Aula, 1977; Rodewald et al., 1977; Gutensohn et al., 1978; Magenis et al., 1978; Reiss et al., 1979; Patil and Hanson, 1980; Dobyns et al., 1985; Brocker-Vriends et al., 1986; Kiss and Osztovics, 1987; Ostergaard and Tommerup et al., 1989; Pecile et al., 1990]. Common manifestations have included growth and mental retardation, congenital heart defect, and minor facial anomalies. In most cases the deletion occurred de novo at 8p21, whereas in a few the 8p deletion was the unbalanced product of a parental reciprocal translocation, inversion or other chromosomal rearrangement [Rosenthal et al., 1973; Kimberling et al., 1975; Guanti et al., 1976; Bass et al., 1983; Smith et al., 1983; Kitatami et al., 1988; Sujansky et al., 1993].

In 1988, a smaller distal 8p deletion, del(8)(p23.1→pter), associated with severe mental retardation, was first observed by Fagan et al. Nine individuals and three members of one family with del(8)(p23.1) were subsequently reported [Hagerman et al., 1988; Fryns

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et al., 1989; Blennow et al., 1990; Pecile et al., 1990; Hutchinson et al., 1992; Pettenati et al., 1992], suggesting that this smaller distal 8p deletion might be relatively common. We now report on three patients with del(8)(p23.1) and describe the clinical manifestations and molecular cytogenetic studies. Although del(8)(p23.1) is associated with fewer phenotypic abnormalities than del(8)(p21), congenital heart defects and mental retardation are still noted.

CLINICAL REPORTS

Case 1 (93-240)

Pregnancy and medical history. This 4-year-old boy was the 3.7 kg product of a term uncomplicated pregnancy delivered by C-section due to breech presentation. Amniocentesis was performed after a low alpha fetoprotein (AFP) result and demonstrated a normal male karyotype. There were no reported neonatal complications. Medical history is significant only for being a quiet baby who slept more than usual, and having recurrent ear infections and fluid in his ears. He was noted to have a bifid uvula, but there were no major malformations or minor anomalies. He sat at 8 months, crawled at 9 months, pulled to stand at 10 months, and walked at 15 months. He said his first word at one year, and at 2 years had a 4-word vocabulary. He has been evaluated for toe-walking and delayed speech and language. He is described as being very active and easily distractable, prompting chromosome and fragile X testing.

Case 2 (90-339)

Pregnancy and medical history. This 5-year-old girl was the 2.3 kg product of a term pregnancy delivered by repeat C-section. Amniocentesis established a normal female karyotype. A murmur was noted at birth, echocardiogram documented two atrial septal defects (ASDs), mild valvular pulmonic stenosis, and mild aortic valve regurgitation. The ASDs were repaired at 18 months. She walked at about 2 years and said her first word at the same time. She had one seizure at age 4¾ years after a fall. A neuropsychological evaluation at 4⅔ years demonstrated mild mental retardation. Examination at age 5 years showed almond-shaped upslanting palpebral fissures, a small head with a narrow forehead, and a flat occiput. Figure 1 shows this patient at age 9 years.

Case 3 (92-531)

Pregnancy and medical history. This deceased girl was the 2.4 kg product of a 38-week twin gestation delivered by repeat C-section. No information is available on the pregnancy. At a few hours of life she was noted to have irregular heart rhythm and investigations showed a hypoplastic left heart with mitral and aortic stenosis and hypoplastic aortic arch. She had multiple minor anomalies, including downslanting palpebral fissures, apparently low-set, posteriorly angulated ears, flat nasal bridge, widely spaced nipples, and puffy feet. She died after surgery and a complicated postoperative course.

Table I summarizes the information on all three patients.

MOLECULAR CYTOGENETIC STUDIES

Chromosome analysis on all three patients was performed using standard cytogentic techniques. Each had a similar distal deletion of the short arm of one chromosome 8: del(8)(p23.1) (Figs. 2, 3). Closer examination suggested that the breakpoints on the deleted chromosome 8 may differ among these patients, although this is uncertain due to the limitation of resolution. In case 1 the breakpoint appears to be distal 8p23.1, whereas in case 3 it is more proximal 8p23.1. Chromosome analysis of the parents of case 1 and mother of case 2 were normal; the remaining parents were not available for study.

Fluorescence in situ hybridization (FISH) analysis with a chromosome 8-specific library, was performed on cases 1 and 2 (Fig. 4, left). These studies indicated that no other rearrangement, such as a small undetectable translocation, was involved. FISH study with a chromosome 8-specific telomere probe also confirmed terminal deletions in cases 1 and 2 (Fig. 4, right). Case 3 was not available for FISH study due to early death.

DISCUSSION

Clinical manifestations in reported patients with chromosome abnormalities involving 8p23.1 are summarized in Table II. There is no sex predilection and no relationship between maternal or paternal age and the occurrence of distal 8p deletions. The patients' ages at diagnosis have varied from infancy to 16 years.

Sixteen patients with distal 8p deletion, del(8)(p23.1), including those described in this study, have been reported since 1988. Most are de novo [Fagan et al., 1988; Hagerman et al., 1988; Fryns et al., 1989; Blennow et al., 1990; Pecile et al., 1990; Hutchinson et al., 1992], except for one family with three affected members [Pettenati et al., 1992]. Three unrelated patients were found within a 3-year period in our laboratory and five cases were found within a 4-year period by another group [Hutchinson et al., 1992], indicating that the distal 8p deletion might be a relatively common chromosomal abnormality.

Clinical findings of 15 patients with deletion of 8p23.1 are variable (Table II). Minor facial anomalies in these patients are not very distinctive. Mental retardation (13/14), behavior problems (10/14), congenital heart defects (6/15), seizures (6/15), and genitourinary anomalies (5/15) have been observed. Different breakpoints within the 8p23.1 region may be responsible for variability of clinical presentation. For instance, major congenital anomalies, especially congenital heart defects, are most often associated with proximal 8p23.1 breakpoints [cases 2 and 3 in this

Fig. 1. Case 2 (90-339) at age 9 years.

study, one case from Pecile et al., 1990, 3 cases from Hutchinson et al., 1992]. Also 4/4 cases with inv dup(8) [Feldman et al., 1993] and 39/42 cases with rec(8) [Sujansky et al., 1993], all with breakpoints at proximal 8p23.1, have been associated with congenital heart defects.

This small deletion is easily overlooked. Our cases 1 and 2 were reported to have normal chromosomes

TABLE I. Summary of Three Patients With del(8)(p23.1)*

	Case 1 (93-240)	Case 2 (90-339)	Case 3 (92-531)
Maternal age (yrs)	31	30	23
Pregnancy history	Unremarkable	"Nerves"	Not available
Prenatal testing	Low AFP, nl. amnio	Nl. amnio	No information
Pregnancy duration	39 weeks	Term	39 weeks
Delivery	C-section/breech	C-section/repeat	C-section/twin pregnancy
Birth weight (g)	3,656	2,268 (SGA)	2,400 twin (SGA)
Development	Mild motor delays Speech delay Behav. problems ADHD	Mild MR Speech delay Behav. problems ADD	Not available
Growth	25–50th centile	25–50th centile	1st centile
Head size	50th centile	2nd centile	Not available
Heart defect	None	2 ASDs Mild valvular PS Mild AV regurg.	HLHS Mitral/aortic stenosis
Minor anomalies	None noted	Flat occiput Narrow forehead Almond-shaped upslanting palpebral fissures	? Downslanting palpebral fissures Flat nasal bridge Apparently low-set posteriorly angulated ears Right cheek skin tag Mild retrognathia Short neck Redundant skin Widely spaced nipples
Genitourinary anomalies	None noted	None noted	Bil. hydroureter-nephrosis
Other findings	Bifid uvula Toe walking	Post-traumatic seizures Abnl. EEG and BEAM	Puffy feet
Parental chromosomes	Both normal	Mother normal Father not available	Not available

*AFP, alpha fetoprotein; SGA, small for gestational age; ADHD, attention deficit hyperactivity disorder; ADD, attention deficit disorder; MR, mental retardation; ASD, atrial septal defect; AV, atrioventricular; PS, pulmonic stenosis; HLHS, hypoplastic left heart syndrome.

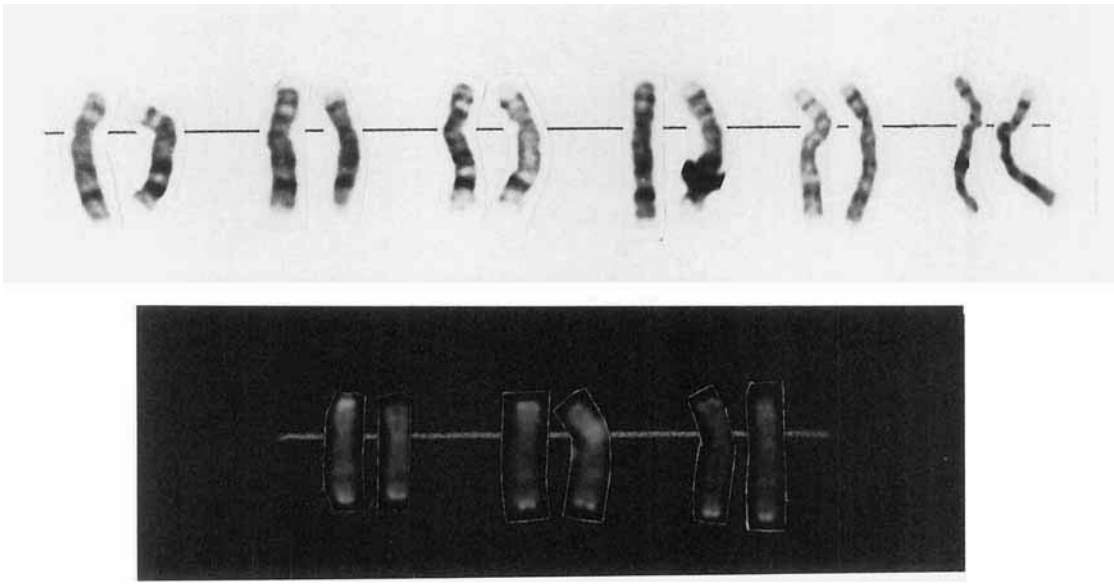

Fig. 2. Cytogenetic studies of case 1 (93-240). Pairs of chromosomes 8 from 6 cells with GTG banding (**upper**) and 3 cells with RFA banding (**lower**) are shown. The deleted chromosome is the right member of each pair. The arrow points to the breakpoint region on the idiogram of chromosome 8 for this case.

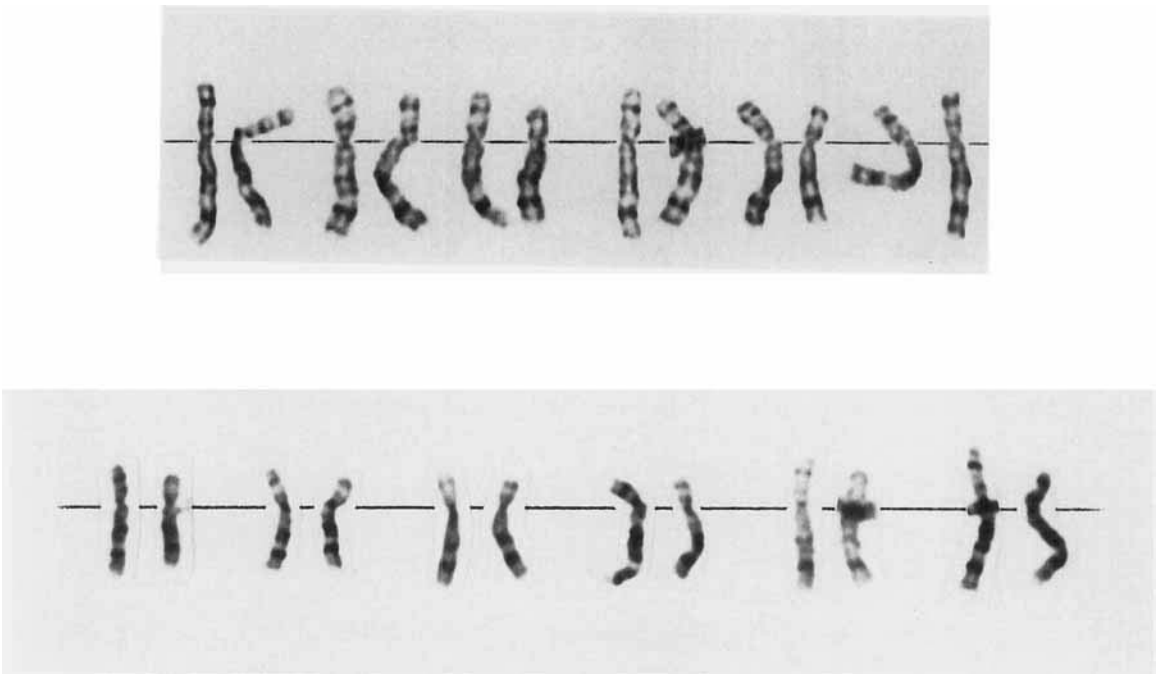

Fig. 3. Cytogenetic studies of case 2 (90-339) and case 3 (92-531). Pairs of GTG-banded chromosomes 8 from 6 cells of case 2 (**upper**) and 5 cells of case 3 (**lower**) are shown. The deleted chromosome is the right member of each pair. The arrow points to the breakpoint region on the idiogram of chromosome 8 for each case.

TABLE II. Clinical Manifestations in Patients With Distal 8p Deletion (8)(p23.1)*

del(8)(p23.1) described by:	Fagan et al. [1988]	Fryns et al. [1989]	Blennow et al. [1990]	Pecile et al. [1990]	Pettenati] et al. [1992]			Hutchinson et al. [1992]					Our cases			Total of 15 deletion
					1	2	3	1	2	3	4	5	1	2	3	
Sex	F[a]	M	F	F	M	F	M	F	M	F	M		M	F	F	
Birth weight (kg)	3.2	3.1	3.4	2.7	3.0	2.8							3.7	2.3	2.4	
Age at diagnosis	14y	9y	16y	1y	8y	11y	34y	8y	3y	4y	2y	2m	4y	5y	2d	
Mental retardation	+	+	+	+	+	−	+	+	+	+	+	+	+	+		13/14
Seizures	+	+	−	−	+	+	−	+	−	−	−	−	−	+		6/14
Behavior problem	−	+	+	+	+	+	−	+	−	+	+	−	+	+		10/14
Cong. heart defect	−	−	−	+	−	−	−	−	+	+	−	+	−	+	+	6/15
Genitourinary anl.	−	+	−	−	−	−	−	−	+	+	+	−	−	−	+	5/15
High/narrow forehead	−	−	+	−	−	−	−	+	−	−	+	+	−	+	−	5/15
Abnormal slanting palpebral fissures	−	−	+	−	−	−	−	−	−	+	−	−	−	+	+	4/15
High/wide flat nasal bridge	−	−	+	+	−	−	−	+	+	+	+	−	−	−	+	7/15
Broad cheeks	−	−	+	+	−	−	−	+	−	+	+	−	−	−	−	5/15
Retrognathia/ small jaw	−	+	+	+	−	−	−	+	+	+	+	+	−	−	+	9/15
App. low-set/ abnormal ears	+	+	−	+	−	−	−	+	−	+	+	+	−	−	+	8/15
Puffy hands/feet	−	−	−	+	−	−	−	+	−	+	+	−	−	−	+	5/15
Broad chest/ wide-set nipples	−	+	−	+	−	−	−	+	+	+	+	−	−	−	+	7/15

*One case reported by Hagerman et al. [1988] is excluded due to insufficient information.
[a]F, female; M, male; y, year; m, month; d, day; blank means information is either not available or not noted.

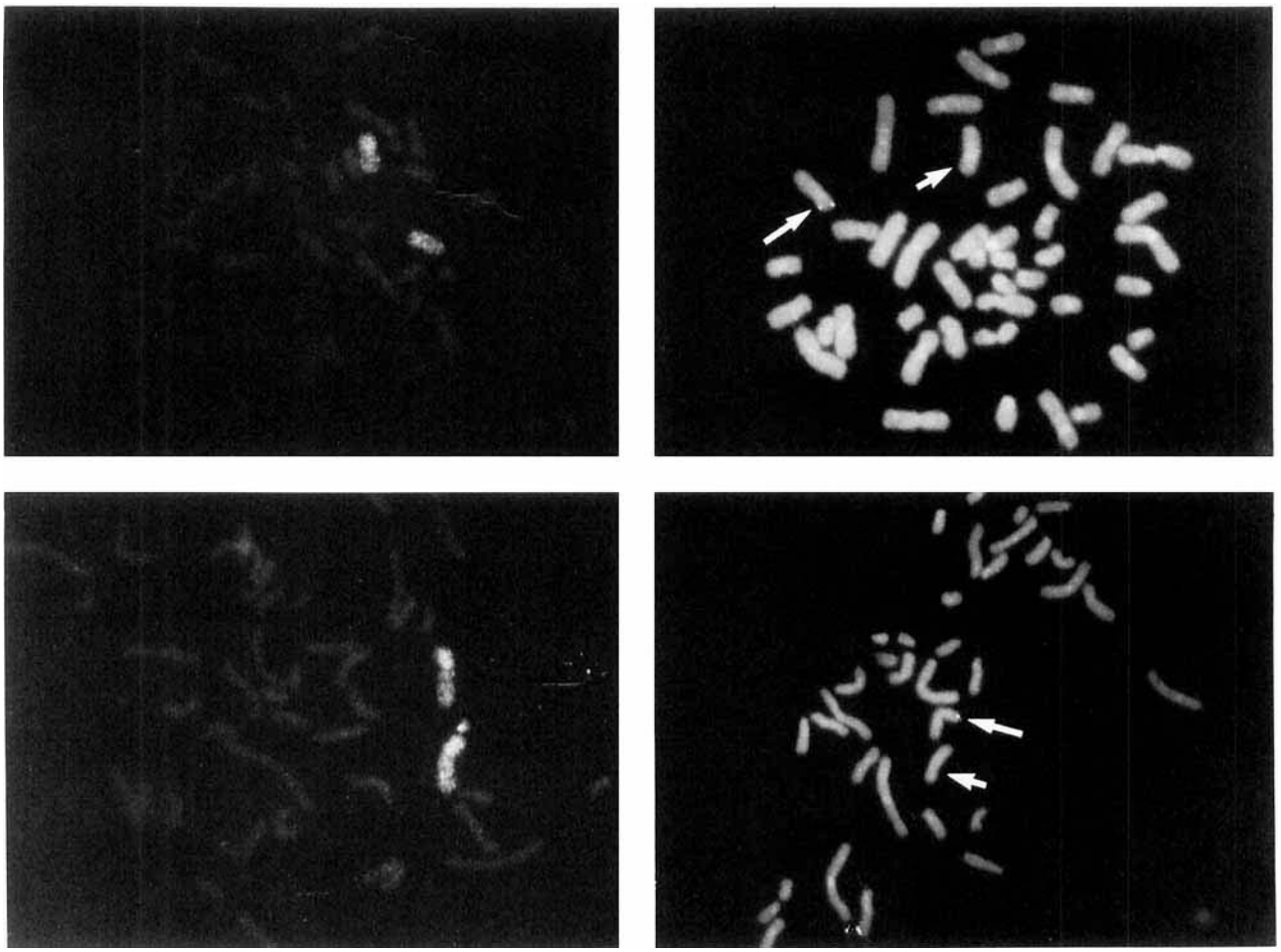

Fig. 4. Fluorescence in situ hybridization (FISH) analysis of case 1 (93-240, **upper**) and case 2 (90-339, **lower**). **Left:** With a chromosome 8-specific paint probe, FISH results showed that both chromosomes 8 were entirely painted and no other chromosome is stained. **Right:** With a chromosome 8-specific telomere probe, FISH results showed that the telomere sequences only hybridized to normal chromosome 8 (large arrows), but not hybridized to deleted chromosome 8 (small arrows), indicating that both patients had terminal deletions. (Note: The normal and deleted chromosomes 8 were identified by DAPI countstaining, which is not shown.)

at amniocentesis. Furthermore, it may be missed clinically since some cases may be associated with few or no major congenital anomalies. Our experience indicates that high resolution G and R banding analysis with attention focused on distal 8p can be helpful in evaluating children with developmental delay, even if prenatal studies had indicated normal chromosomes. Furthermore, FISH with an 8p-specific telomere probe provides convincing confirmation of distal 8p23.1 deletion.

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